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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,644	MARTIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/05 has been entered.

2. Claims 52-84 are pending and under examination in the instant application as they read on a method of regulating an inflammation or cellular secretory process (granule release) in a subject comprising administering a composition comprising a MANS peptide or an active fragment thereof wherein inflammation is respiratory diseases and COPD as the species.

3. Applicant's IDS, filed 10/31/05, is acknowledged.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 55-56, 64-75 and 76-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "a membrane-bound vesicle in an infiltrating inflammatory cell in a subject" claimed in claim 64, "provoked by said inflammatory mediator in a subject" claimed in claims 55, line 2, 68, line 2 and 76, line 2 and line 6 and " wherein said inflammatory mediator results in inflammation caused by inflammatory airway diseases" claimed in claims 56, 69 and 77 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 10/31/05 points to the specification at ¶12, ¶39 and ¶42 for support for the newly added limitations "a membrane-bound vesicle in an infiltrating inflammatory cell in a subject" claimed in claim 64, "provoked by said inflammatory mediator" as claimed in claims 55, 68, and 76 and " wherein said inflammatory mediator results in inflammation caused by inflammatory airway diseases" claimed in claims 56, 69 and 77. However, the specification does not provide a clear support for such limitation. Applicant directs the Examiner's attention to ¶39 for support for the new limitation of claim 64, while ¶39 discloses that a number of cellular secretory processes involve the release of contents from membrane-bound vesicles, there

is not disclosure that such a membrane-bound vesicle exist in an infiltrating inflammatory cells as claimed. Further, It is noted that ¶12 discloses that it is known that a wide variety of agents and inflammatory/humoral mediators provoke mucin secretion. No method of inhibiting the release of an inflammatory mediator and mucus secretion provoked by inflammatory mediator using the claimed peptide is found. Obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

6. Claims 52-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for a method of inhibiting the release of an inflammatory mediator in a subject comprising: administering to a subject suffering from inflammation a therapeutically effective amount of a pharmaceutical composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1, in an amount effective to block the release of mediators of inflammation secreted from infiltrating inflammatory cells at a site of inflammation in the subject in claim 52 or a method of inhibiting the release of an inflammatory mediator from a membrane-bound vesicle in an infiltrating inflammatory cell in a subject suffering from inflammation caused by a disease or condition involving inflammation comprising: administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising a MANS peptide consisting of an amino acid sequence of SEQ I DNO: 1 in an amount effective to inhibit said release of said inflammatory mediator from said vesicle in said inflammatory cell in the subject in claim 64, or a method of inhibiting the release of an inflammatory mediator and mucus secretion provoked by said inflammatory mediator in a subject comprising: administering to a subject suffering from inflammation a therapeutically effective amont of a pharmaceutical composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1, whereby the release of inflammatory mediators and mucus secretion in the provoked by said inflammatory mediator subject are reduced compared to that which would occur in the absence of said pharmaceutical composition in claim 76. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification fails to provide empirical data to show that method would work in vivo.

At issue, whether 1) the claimed methods would work in vivo, 2) the claimed methods would inhibit any inflammatory mediator release, 3) the claimed method would inhibit the release of an inflammatory mediator from membrane-bound vesicle in an infiltrating cells, or 4) the claimed method would inhibit the release of an inflammatory mediator and mucus secretion provoked by said inflammatory mediator.

Issue number 1, the state of the art is that current treatments of diseases associated with airway mucus hypersecretion, such as cystic fibrosis, asthma, and bronchitis, do not take into account the homeostatic role of pulmonary mucus, and the impact of mucus on respiratory phathophysiology. According to Rogers, 2003, optimal treatment should aim at the reversion to normal levels of secretion, rather than merely to inhibit hypersecretion (see page 178). Further, Barnes PJ. (Novartis Found Symp. 248:237-49; discussion 249-53, 277-82, 2002, IDS Ref. No. 2) discusses the current and future therapies for airway mucus hypersecretion. Barnes teaches that several novel targets involved in mucus hypersecretion have recently been identified, including epidermal growth factor receptors, MARCKs, Ca2+-activated Cl- channels and mitogen-activated protein kinases. However, the clinical benefits from inhibiting mucus hypersecretion are still not certain, casting some doubts on this therapeutic approach (see abstract page 237 in particular). While the specification relies upon inhibiting mucin secretion with SEQ ID NO:1 as an assay for MANS peptide activity (see paragraph 71 of the instant specification), no such efficacy is disclosed. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Issue numbers 2 and 3, the specification only discloses the ability of MANS peptide to block secretion of myloperoxidase from isolated human neutrophils. Besides MPO, inflammatory mediator, the specification fails to disclose such inflammatory mediators, can be released by the MANS peptide. There are still numerous inflammatory mediators encompassed in the claim, besides MPO. Further, the specification fails to disclose that, for example, inflammatory mediators such as MPO, TNF and interleukins are mediated by incorporation of secretory vesicle membrane carrying Mac-1 and/or L-selectin, into the plasma membrane of a cell such as a neutrophil. While the secretory vesicles constitute a reservoir of membrane-associated receptors needed at the earliest phases of the neutrophil-mediated inflammatory response, secretory vesicles are mobilized in response to a wide variety of inflammatory stimuli. The membranes of secretory vesicles are rich in the Mac-1, CR3, the complement receptor 1, receptors for formylated bacterial peptides, the LPS/lipoteichoic acid-rector CD14, the FcγIII receptor CD16 and the metalloprotease leukolysin, all of which are incorporated in the plasma membrane after exocytosis. However, the specification fails to demonstrate that all these inflammatory mediators are carried by the same membrane-bound vesicle in an infiltrating inflammatory cell, so that the release of one indicates a release of all at the same time. The examiner notes that alkaline phosphatase activity resided in light-density membrane vesicles (i.e., location of secretory granules), which are distinct from specific, azurophil containing MPO, and large granules.

Issue number 4, it has not been shown either by the specification or in the art that for example, mypoperosidase (MPO), an inflammatory mediator, would provoke the release of itself, i.e., MOP. Further, even if that happens, inhibiting the release of MPO would lead to the inhibition of further down stream activity of the MPO, such as provoking the release of itself as claimed in claim 76.

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence

which is reasonably predictive that the claimed methods are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

Applicant's arguments submitted 10/31/05, has been fully considered, but have not been persuasive.

Regarding, the issue of reducing/inhibiting an inflammatory mediator, Applicant submits that Figures 9 and 10 provide in vitro evidence of a dose-dependent response where MANS peptide reduces the level of MPO (myeloperoxidase), an inflammatory mediator, in activated neutrophils and Figures 11-15 provide data that MPO secretion can be stimulated in human and canine neutrophils.

However, the specification provides no evidence that the claimed basophils, eosinophils, monocytes or leukocytes would respond to MANS peptide and can inhibit the release of any inflammatory mediators in the same manner as in the activated neutrophils by blocking PKC/PKG activation.

Regarding the *in intro/ in vivo* models, Applicant directs the examiner's attention to the MPEP 2164.02. Applicant submits that the claims are directed to administering MANS peptide with a specific sequence to a subject to block the release of inflammatory mediators and that MPO is an inflammatory mediator and neutrophils are inflammatory cells. Applicant further submits that that neutrophils are recognized as being correlated to inflammation. Applicant draws the Examiner's attention to Dr. Kenneth Adler's declaration, which states that in vitro studies with granulocytes, which includes neutrophils and eosinophils, are predictive of the outcome of inflammatory diseases in vivo. Applicant submits that these publications are indicative that one skilled in the art would accept the in vitro model of studying stimulated neutrophils as reasonably correlated to inhibiting the release of an inflammatory mediator in a subject. Applicant submits that said declaration provides two publications where granulocytes are used in *in vitro* studies and relied upon as predictive of *in vivo* outcome by the authors. Applicant submits that these publications are indicative that one skilled in the art would accept the *in vitro* model of studying stimulated neutrophils as reasonably correlated to inhibiting the release of an inflammatory mediator in a subject.

However, Haile et al reference is using vinblatine, which belongs to the group of drugs called plant alkaloids, i.e., microtubule inhibitors, while the instant invention is using MANS peptide of SEQ ID NO: 1 that inhibits PKC/PKG activation (i.e., the mechanism of action are different). Therefore, Haile et al reference is not analogo to the issue at hand, and therefore is irrelevent to the claimed invention. Vinblastine would stibilze the microtubules and prevent organale translocation from the pernuclear region to the cell membrane via microtubules. In contrast, the MANS peptide acts by inhibiting PKC/PKG activation and prevent the tethering of granules to the cellular contractile apparatus, mediating granule movement to the cell periphery and subsequent exocytotic release. The release of an inflammatory mediators and mucin in the instant

case is mircrotuble independent. Therefore the mechanisms of action of vinblastine is different than the claim peptide.

Haile et al further raises a new issue that eosinophil lysis and release of free granules may be more important than intact cell degranulation for the release of mediators (see page 899, 2nd col., 1st paragraph in particular). Haile et al teaches that even though we did not observe these alterations in the bronchial submucosa, the presence of degenerating eosinophils and of granule exocytosis in the bronchial lumen supports this hypothesis. Therefore, it is unpredictable whether the claimed peptide would be effective in vivo in accomplishing the claimed method since eosinophily lysis and release of free granules is more important than intact cell degranulation using the claimed peptide.

Applicant further addresses the Examiner's concern regarding the correlation of *in vitro/in vivo* models. Applicant refers to Dr. Adler's declaration on paragraph 8 for support that granulocytes are used in vitro model of studies are relied upon as predictive of in vivo outcome by the authors. On paragraph 8, of the declaration Dr. Adler directs the Examiner's attention to a publication by Abdel-Latif et al, showing that neutrophils isolated from mice with a targeted gene deletion maintain this deletion *in vitro* and thus function as they would *in vivo*. Applicant further refers to Dr. Adler's declaration on ¶9, wherein Dr. Adler refers to Lacy et al publication showing that isolated granulocytes from asthmatic patients responded differently in vitro, mimicking their in vivo aberrations.

However, (1) knockout gene in transgenic mice is not structurally analogous to administering a peptide to a subject. (2) the binding activities/kinetics of the peptide and a knockout gene are not similar. (3) In many cases when you take a cell from *in vivo* to *in vitro* environment the cells are responsive as the case in all experimental cell lines and primer culture, however, the issue here is vice versa. When you administer the peptide to the inflammatory mediator cell *in vitro* would have the same efficacy *in vivo*.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 52-62, 64-74 and 76-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15.

Adler et al teach that the mucin hypersecretion provoked by the pathophysiological relevant secretagogue, uridine triphosphate, or by a combination of PMA+ 8 bromo-cGMP, was inhibited in a concentration-dependent manner by a synthetic peptide with a identical to the myristic acid containing N-terminal region of MARCKS protein, the site of its attachment to granule membranes. Adler et al teach that the PKC inhibitor, calphostin C, the cGMP inhibitor, Rp-8-Br-PET-cGMP, or the phospatase inhibitor, okadaic acid, independently inhibited mucin secretion provoked by the mentioned secretagogues (see the entire document). Further, as is evidenced by the specification on page 26, lines 11-15, that the MANS peptide consisted of sequence identical to the first 24 amino acids of MARCKS, i.e. the myristoylated N-terminal region that mediates MARCKS insertion into membranes (claimed SEQ ID NO:1). Further, Adler et al teach that hypersecreation of mucus contributes to air way inflammation and obstruction in COPD. Adler et al further teach that the MARCKS protein is a major cellular substrate for protein kinase C, is a central, convergent intracellular molecule controlling release of mucine granules by airway goblet cells.

The claimed invention differs from the reference teachings only by the recitation that the method of inhibiting an inflammatory mediator in a subject in claims 52, 64 and 76 wherein the subject is a mammal in claims 57, 71 and 78, wherein the mammal is selected from the group consisting of humans, canines, equines and felines in claims 58, 72 and 79.

While the prior art teachings may be silent as to the "inflammatory mediator" per se; the method, the product used in the reference method are the same as the claimed method. Therefore "inflammatory mediator" is considered inherent properties of the referenced method.

Given that hypersecreation of mucus contributes to air way inflammation and obstruction in COPD and that MARCKS protein is a major cellular substrate for protein kinase C, is a central, convergent intracellular molecule controlling release of mucine granules by airway goblet cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to consider practice the method taught by Adler et al in mammalian subject including humans.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the inhibition of mucin secretion alleviate hypersecretion of mucus cause by airway inflammation taught by Adler et al and further, Adler et al suggest the in vivo treatment implicitly.

Claims 59, 60, 62, 73, 74, 80-81 and 84 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the administering routs and formulation to regulate inflammation and mucin secretion in humans. Especially, since the condition is airway inflammation, pulmonary administration would be the target. Further, it has

been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments submitted 10/31/05, has been fully considered, but have not been found persuasive.

Applicant submits that the Examiner is erroneously relying on the first sentence of the Adler abstract for motivation to support his position that the claims are bvious over the Adler abstract. Applicant submits that the sentence "hypersecretion of mucus contributes to airway inflammation and obstruction in COPD" was not intended to establish a scientific link between mucus secretion and inflammation. Dr. Adler is an expert in the respiratory field, and in his attached declaration, ¶3, he explains that there is no direct link between excess mucus and inflammation, and that mucus secretion does not cause inflammation. Dr. Adler qualifies what he meant by his sentence in that excess mucus can, if it allowed to build up, make the airways susceptible to microbial infection, which in turn can possibly results in inflammation. Applicant submits that Dr. Adler makes it clear that mucus secretion and inflammation are two separate processes.

It should be noted that Dr. Adler is an inventor on the instant application, the real party interest in this application, and thus is a concerned party. Dr. Adler is unquestionably an expert, but the specification on page 1, ¶8 and ¶9 establish a scientific link between excess mucus/inflammatory mediators and inflammation. The specification discloses the same sentence that hypersecretion of mucus contributes to the pathogenesis of a large number of airway inflammatory diseases in both human and non-human animals. Further, increased mucus secretion is seen in chronic disease states such as COPD. The specification on page 1, ¶9 discloses that accompanying hypersecretion of mucus in many of these respiratory diseases is the constant presence of inflammatory cells in the airways. These cells contribute greatly to the pathology of these diseases via the tissue damage done by the inflammatory mediators released from these cells. Therefore, the inflammatory mediator (e.g. MPO) which accompanying hypersecretion of mucus through the inflammatory cells in the airway, contributes to airway inflammation by inducing the desquamation of airway epithelial tissue. Further, According to Dr. Adler's declaration, the excess mucus in the airway makes the individual more susceptible to microbial infection, which then can possibly result in inflammation that is caused by the microbial infection. However, since excess mucus is a media for microbial infection, which result in inflammation, it would be desirable to inhibit the excess mucus, so that no microbial infection will exist, as a result treating inflammation.

Applicant refers to Dr. Adler's declaration on ¶4, a person skilled in the art, such has himself, would not be motivated by his own abstract, to treat inflammation by blocking the release of inflammatory mediators, with a synthetic peptide of the myristic acid containing N-terminal region of MARCKS protein.

However, once the skilled armed with knowledge that accompanying hypersecretion of mucus is the constant presence of inflammatory cells in the airway, wherein these cells contribute greatly to the pathology of these diseases via the tissue damage done by inflammatory mediators released from these cells. The skilled artisan would be motivated to inhibit hypersecretion of mucus which is accompany the presence of inflammatory cells in the airway, which contribute greatly to the pathology of these diseases via the tissue damage done by inflammatory mediators released from the inflammatory cells. Further, given that excess mucus in the airways makes the individual more susceptible to microbial infection, which then can possibly result in inflammation that is caused by the microbial infection, the skilled in the art would have been motivated to inhibit the excess mucus in the airway to prevent inflammation caused by microbial infection.

Applicant refers to ¶5 of Dr. Adler's declaration, which provides further supports by citing Haile et al which confirms that mucus secretion is not associated with inflammation. Applicant concludes that the Adler abstract only discloses mediating mucus secretion with this synthethic peptide and does not suggest that treating or mediating inflammatory as suggested by the Examiner.

Haile *et al* teachings that mucus secretion is independent of the presence of granulocytes and neutrophils (page 892, 1st col., 1st sentence of bridging paragraph) appears to be at odds with the Applicant's disclosure that accompanying hypersecretion of mucus in many of these respiratory diseases is the constant presence of inflammatory cells in the airways (page 1, ¶8). Since the instant claims were drafted based on the specification disclosure, the skilled artisan still would not have a reasonable expectation that the claimed method would lead to a desirable endpoint of inhibiting the release of an inflammatory mediator secreted from infiltrating inflammatory cells at a site of inflammation in the subject. Nor would it demonstrate that the specification did provide an enabling disclosure of inhibiting the release of inflammatory mediator and mucus secretion commensurate in scope with the instant claims, which encompass the inhibition of the release of an inflammatory mediator and mucus secretion in asthma.

Applicant submits that Adler abstract does not specifically recite that mucus secretion is mediated by the MANS peptide having the sequence of SEQ ID NO: 1, as now claimed in all of the presently pending claims. Applicant submits that rather, the abstract states that mucin hypersecretion was inhibited by a synthetic peptide of the myristic acid containing N-terminal region of MARCKS protein. Applicant submits that a skilled person reviewing the abstract would not specifically be able to determine that MANS peptide with a specific 24 amino acid sequence was the peptide that was used to mediated mucin secretion. Applicant concludes that Adler abstract does not render the claimed invention obvious.

Contrary to Applicant assertion, Adler et al teaches that mucin hypersecretion provoked by the pathophysiologically relevant secretagogue was inhibited in a concentration-dependent manner by a synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of MARCKS protein, the site of its attachment to granule membranes. The synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of MARCKS protein is the claime SEQ ID NO:1 as is evidenced by the specification on page 26, lines 11-15, that the MANS peptide consisted of sequence identical to the first 24 amino acids of MARCKS, i.e. the myristoylated N-terminal region that mediates MARCKS insertion into membranes (claimed SEQ ID NO:1).

Applicant submit that if their own application is not enabled, which the Examiner alleges because there are no in vivo examples, then to be consistent with that principle, the Adler abstract should also not be considered to be enabled because it does not contain any in vivo examples for inhibiting the release of an inflammatory mediator.

However, in circumstances such as this, where the specification does not appear to add anything not taught by the prior art, the examiner may not have sufficient evidence to determine which rejection is more appropriate, i.e., the art rejection or the enablement rejection. If the specification is enabling, so is the prior art reference and vice versa. In the instant case the specification teachings appear to commensurate with the disclosure of Adler et al abstract. If the specification is enabling, so to is the reference, and the claims may be unpatentable over the teachings of the reference. If the reference is not enabling, neither is the specification, and the claims may again be unpatentable. The Examiner need not choose based on the limited evidence the rejection that is the more correct one, as the result is the same in either instance-the claims are unpatentable. It is thus proper for the examiner to make the superficially inconsistent art and enablement rejections, and place the burden on applicant to distinguish his or her specification from the prior art and to point out how the specification goes beyond and elaborates upon what is taught by the previously published reference. The Examiner has not been told why the teachings of the specification present anything more than is taught by Adler et al reference.

The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in the first instance. In a case such as this, if only the prior art rejection was made, and Applicant shows that the reference is not enabling and base on an "obvious to try" standard, the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, Applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicant also argue that Adler et al abstract actually provides a negative teaching, for one skilled in the art that would be led away from a therapeutic application of the present invention, particularly for the treatment of lung disease, because the abstract teaches that the N-terminal

region of the MARCKS protein antagonize UTP. Applicant points that UTP is well known as a therapeutic compound for treating lung diseases, including "cystic fibrosis, chronic bronchitis, asthma and brochiectasis" US. Pat. No. 5,292,498). Given the known therapeutic activity of UTP, person of ordinary skill in the art would be reluctant at best to utilize an antagonist thereof as a therapeutic agent, such as for the treatment of lung disease.

However, UTP is not claimed and UTP does not address the issue at hand and considered irrelevant to the claimed invention. The issue here the peptide of SEQ ID NO: 1. Here in contrast to applicant's assertions of teaching away by the prior art because the references indicate a successful method of inhibiting mucin hypersecretion provoked by the pathophysiologically relevant secretagogue, uridin triphosphate, or by a combination of PMA + 8 bromo-cGMP, in a concentration-dependent manner by a synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of MARCKS protein; there is no discouragement nor skepticism in the prior art for using said peptide in the inhibition of mucin hypersecretion. The instant claims do not use combination therapy of UTP and SEQ ID NO:1 in the claimed method so that the skilled artisan would be discouraged from following the path set out in the reference.

Applicant note that the present invention relates to methods of inhibiting **inflammatory mediators released from inflammatory cells** and **not epithelial cells** as recited in the Adler abstract. Applicant submits that it is well known in the art that **epithelial cells and inflammatory mediators are different** from one another (emphasis added by Applicant).

It is noted that infiltrating inflammatory cells that release inflammatory mediators accompany the epithelial cells mucus secretion at the site of inflammation. Therefore, it is clear that both Adler et al. and applicant administer the same composition comprising the same peptide to the same subject to achieve the same results. Applicant relies upon said observation but does not provide objective evidence that the prior art teaching of treating the same inflammation with the same compositions to achieve the same therapeutic effect differs from the claimed methods. Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

9. Claims 63, 75 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15, as applied to claims 52-62, 64-74 and 76-83 above, and further in view of U.S Patent No. 6,506,779 of record.

The teachings of Adler et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only in that they do not teach the administration of a second molecule of an antibiotics or antiviral in claims 63, 75 and 84.

The '779 patent teaches a method of for treating inflammatory processes and diseases comprising administering an inhibitory compound which is used in combination with one or more antibiotic, and/or antiviral therapeutic agents. The `779 patent further teaches that such agents can be used when a multi-fold treatment of pain and inflammation is desired (see column 12, line 11-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combined the MANS peptide of SEQ ID NO: 1 with the antibiotic or antiviral compound taught by the `779 patent, were known to alleviate inflammation, as taught by the '779 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the antibiotic or antiviral compound taught by the `779 patent because the antibiotics are known to treat inflammation and said combination of additional antibiotics or antiviral would be considered obvious. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

Applicant's arguments submitted 10/31/05, has been fully considered, but have not been found persuasive.

Applicant argues that the `779 patent relates to acetylene derivatives, methods of treatment and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases. It does not in any way discuss or even contemplate the MANS peptide or a MARCKS related protein. Applicant submits for the same reasons above the Adler abstract either alone or in combination fail to contain any motivation to combine their teachings as required by In re Sang-su Lee.

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims would have been obvious as a matter of law under 35 U.S.C 103(a).

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 52-62, 64-74 and 76-83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 77-79, 82-87, 89-90, 95-96, 98-103 and 105-106 of copending Application No. 09/914,020. Although the conflicting claims are not identical, they are not patentably distinct from each other because although the instant claims are drawn to methods of inhibiting inflammatory mediators released from inflammatory cells while the `020 application claims are drawn to methods of inhibiting mucus secretion by a mucus-secreting cell from epithelia cells using the same peptide of SEQ ID NO:24, both the instant claims and the `020 application claims drawn to the treatment of the same patient populations with the same compositions to achieve the same therapeutic effect. Specially because both epithelial cells and inflammatory cells inherently present together during inflammation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 63, 75 and 84 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 77-79, 82-87, 89-90, 95-96, 98-103 and 105-106 of copending Application No. 09/914,020 in view of U.S Patent No. 6,506,779 of record.

The teachings of claims of the `020 applicant have been discussed, supra.

The claimed invention differs from the reference teachings only in that they do not teach the administration of a second molecule of an antibiotics or antiviral in claims 63, 75 and 84.

The '779 patent teaches a method of for treating inflammatory processes and diseases comprising administering an inhibitory compound which is used in combination with one or more antibiotic, and/or antiviral therapeutic agents. The `779 patent further teaches that such

agents can be used when a multi-fold treatment of pain and inflammation is desired (see column 12, line 11-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combined the MANS peptide of SEQ ID NO: 1 with the antibiotic or antiviral compound taught by the `779 patent, were known to alleviate inflammation, as taught by the '779 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the antibiotic or antiviral compound taught by the `779 patent because the antibiotics are known to treat inflammation and said combination of additional antibiotics or antiviral would be considered obvious. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

This is a provisional obviousness-type double patenting rejection.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 6, 2006

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